

REMARKS / ARGUMENTS

Claims 1, 2 and 4-12 are pending in the application and stand rejected. In view of the following discussion, the applicants submit that all pending claims are in condition for allowance.

On page 2 of the Office Action the Examiner rejected claim 12 under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The applicants respectfully traverse the rejection. The applicants submit the claimed range does not have to be explicitly taught in the specification. Rather, the Examiner should take into account which ranges a skilled artisan would consider inherently supported by the discussion in the original disclosure. MPEP § 2163.05(III) and *In re Wertheim*, 541 F.2d 257 (CCPA 1976). The language “about 0.15 to about 0.18 percent” is supported on page 3 of the specification, and at a minimum inherently supported by the specification and thus is not new matter. The claimed range complies with the written description requirement and is allowable. Accordingly, the applicants request the Examiner withdraw the rejection.

On page 3 the Examiner rejected claims 1-2, 4, 6 and 12 under 35 U.S.C. § 103(a) as being unpatentable over Adjei et al., (U.S. Pat. No. 6,261,539). The applicants respectfully traverse the rejection. The Examiner alleges the range of water content in Adjei disclosing 300-2000 ppm encompasses the claimed range of 0.13 to 0.18% (equivalent to 1300 to 1800 ppm). Applicants submit the broad range of 300-2000ppm in Adjei does not disclose or suggest the narrow claimed range of water content having the superior properties of claim 1. The specific water content of claim 1 provides unexpected superior results in reproducibility of actuation events. A showing that the claimed range achieves unexpected results relative to the prior art range rebuts a *prima facie* case of obviousness based on claimed ranges that overlap or lie inside ranges disclosed by the prior art. *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

The Examiner alleges, on pages 15-16 of the Office Action, that the data submitted in the Declaration of George DeStefano (“DeStefano Declaration”) does not indicate that actuation events, measured as amount of albuterol sulfate recovered in the spray volume, are more consistent at the claimed water content range, but instead shows that the fluctuations are similar in cans of differing water contents, including containers having 1200 and 4000 ppm. The Examiner specifically pointed to fluctuations of 85.73 to 138.10, 74.83 to 116.7, and 99.24 to

122.24 in cans containing 1200 ppm, 4000 ppm and 1500 ppm water, respectively. The applicants submit the Examiner has selected two of the more extreme values for each can, and compared only two actuation events. Therefore the fluctuations appear to be inordinately large.

A statistically sound approach to determine the consistency of a series of actuation events in a single can is to calculate the standard deviation for all of the actuation events, as discussed below. Analyzed in this way, cans containing 1500 ppm and 4000 ppm water have unexpectedly very consistent reproducibility and much less fluctuation as compared to cans containing inherent to 1200 ppm water or less. Such results, based on the analysis of all of the actuation events rather than only two, are very different than those indicated by the Examiner.

The data in the DeStefano Declaration clearly shows that fluctuations of the single actuation events are very different between certain cans of differing water contents and that the formulations in cans containing 1500 ppm and 4000 ppm water were unexpectedly superior in terms of actuation reproducibility to cans containing 1200 ppm water or less. The standard deviations, calculated from the data presented on pages 2 to 19 of the DeStefano Declaration, for single actuation events of albuterol sulfate (measured in μg of albuterol sulfate recovered) in all of the upright cans containing 300 (inherent), 800, 1000 or 1200 ppm water were determined to be 46.3, 51.1, 36.0 and 47.7, respectively. In the inverted cans containing 300 (inherent), 800, 1000 or 1200 ppm water, the standard deviations were calculated to be 61.3, 30.3, 40.1 and 16.8, respectively. Fluctuation between single actuation events was unexpectedly reduced in upright cans containing 1500, 2500, 3000, 3500 or 4000 ppm where the standard deviations were calculated to be 7.4, 8.1, 9.3, 9.9 and 13.3, respectively. In inverted cans containing 1500, 2500, 3000, 3500 or 4000 ppm the standard deviations were calculated to be 6.1, 4.3, 3.7, 4.5 and 5.5, respectively. The analysis illustrates that the consistency of % reproducibility in cans having a water content of 1500 – 4000 ppm was superior to cans having water content of 1200 ppm or below. This comparison clearly indicates that simply adding water above inherent levels does not always result in improved consistency. It was unexpected that such a large improvement of consistency of % reproducibility could have been achieved at water content levels between 1500 and 4000 ppm.

The Examiner also alleges that the data merely supports the teachings of Adjei (i.e., that the addition of water reduces the fluctuations in actuation events). In light of the above discussion, one skilled in the art viewing Adjei would not expect that water content as claimed

would have such a profound effect on actuation reproducibility. Water content is not identified in Adjei as an important factor for this characteristic. According to Adjei, the water content can be the same whether the active ingredient is albuterol or ipratropium. One skilled in the art would be led to believe water content is not an important factor in achieving reproducibility. Thus, claim 1 is not obvious in light of Adjei. Claims 2, 4, 6 and 12 which depend from claim 1 are also not obvious and are therefore allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

On pages 5-7 the Examiner rejected claims 1-2, 4, 6 and 12 under 35 U.S.C. § 103(a) as being unpatentable over Lewis et al. (EP 1219293); and over Ashurst et al. (U.S. Pat. No. 6,511,652). The applicants respectfully traverse the rejections. For reasons similar to those discussed above, and those discussed in previous responses incorporated herein by reference, none of the references teach or suggest the claimed invention. None of the references teach or suggest the superiority of the claimed range of water of the invention of claim 1 to result in a significantly better SAR for “cans” containing albuterol sulfate and ipratropium bromide with a water content of 1300 to 1800 ppm to release the same amount of albuterol sulfate (i.e., % of theory) during each single actuation event. None of these references would lead a skilled artisan to conclude the claimed range of water content would have a significant effect on the SAR. Therefore, claim 1 is not obvious over Lewis or Ashurst and is allowable. Claims 2, 4, 6 and 12 which depend from claim 1 are also not obvious and are therefore allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejections.

On page 9 the Examiner rejected claims 1-2, 4 and 6 under 35 U.S.C. § 103(a) as being unpatentable over Keller et al. (U.S. Pat. 6,475,467). The applicants respectfully traverse the rejection. For reasons similar to those discussed above, and those discussed in previous responses incorporated herein by reference, Keller does not teach or suggest the claimed invention. Keller does not teach or suggest the superiority of the claimed range of water of the invention of claim 1 to result in a significantly better SAR for “cans” containing albuterol sulfate and ipratropium bromide with a water content of 1300 to 1800 ppm to release the same amount of albuterol sulfate (i.e., % of theory) during each single actuation event. Keller does not lead a skilled artisan to conclude the claimed range of water content would have a significant effect on the SAR. Therefore, claim 1 is not obvious over Keller and is allowable. Claims 2, 4 and 6

which depend from claim 1 are also not obvious and are therefore allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

On page 10 the Examiner rejected claims 5 and 7-11 under 35 U.S.C. § 103(a) as being unpatentable over Adjei et al. in view of Jager et al. (WO 9413262). The applicants respectfully traverse the rejection. For reasons similar to those discussed above, and those discussed in previous responses incorporated herein by reference, the combination of the references does not result in the claimed invention. Adjei alone or in combination with Jager does not teach or suggest the claimed water content of claim 1 that results in unexpected reproducibility as discussed above. Since the combination of Adjei and Jager does not result in claim 1, dependent claims 5 and 7-11 cannot be obvious over Adjei in view of Jager and are thus allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

On page 11 the Examiner maintained the rejection of claims 5 and 7-11 under 35 U.S.C. § 103(a) as being unpatentable over Lewis et al. in view of Jager et al. (WO 9413262). The applicants respectfully traverse the rejection. For reasons similar to those discussed above, and those discussed in previous responses incorporated herein by reference, the combination of the references does not result in the claimed invention. Since the combination of Lewis and Jager does not result in claim 1, dependent claims 5 and 7-11 cannot be obvious over Lewis in view of Jager and are thus allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

On page 13 the Examiner rejected claims 1-2, 4-12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Pat. No. 6,423,298 in view of Adjei et al. The applicants respectfully traverse the rejection. For reasons similar to those discussed above, and those discussed in previous responses incorporated herein by reference, the claimed invention is not obvious over the combination of the references. The combination of the references cannot teach a skilled artisan the claimed water content that results in unexpected reproducibility as discussed above. Therefore, the combination of the '298 patent and Adjei does not result in the claimed invention. Thus, claims 1, 2 and 4-12 are not obvious over the '298 patent in view of Adjei and are therefore allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

Applicants submit that all claims pending in the patent application are in condition for allowance. Accordingly, both reconsideration of this application and its swift passage to issuance are earnestly solicited. In the event there are any fees due and owing in connection with this matter, please charge same to our Deposit Account No. 11-0223.

Respectfully submitted,

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